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# First Reported Outbreak of Diarrhea Due to Adenovirus Infection in a Hematology Unit for Adults

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**Numerous outbreaks of adenovirus infection from different types of health care settings, except a hematology unit, have been reported. This is the first report describing an outbreak of adenovirus infection causing diarrhea among adult hematopoietic stem cell transplant recipients. Six of 21 patients from the outbreak cohort were affected with diarrhea. Electron microscopy, cell culture, and direct DNA sequencing of amplicons generated from stool and blood samples were used to investigate this outbreak. Electron microscopy and cell culture detected adenovirus in stools from symptomatic patients. DNA sequencing of amplicons generated from stool samples confirmed nosocomial transmission of infection from a single index case. The outbreak strain was also detected in plasma of four of these patients, suggesting systemic infection. The outbreak strain was identified as type 12. Standard infection control measures were effective to control this outbreak.**

Adenoviruses are unenveloped DNA viruses. There are at least 51 distinct human adenovirus serotypes. These types are classified into six species, A to F, based on their ability to agglutinate red blood cells (25). Most human disease is associated with only one-third of the known serotypes. Adenoviruses are associated with various sporadic to epidemic infections of the eyes and respiratory and gastrointestinal systems. Adenoviruses cause infections among all age groups, particularly young children. Most of these infections are subclinical, and symptomatic infections are mild and self-limiting with occasional mortality in healthy individuals (27). However, adenoviruses can cause severe disease in most organs of the body in immunocompromised patients, i.e., pneumonia, hepatitis, meningoencephalitis, acute hemorrhagic cystitis, and myocarditis (19, 31). Viremia, prolonged viral shedding, morbidity, and mortality associated with adenovirus infection can be high in such patients. Among immunosuppressed patients, the infection may be acquired de novo, but most clinical manifestations of adenoviruses are due to reactivation of latent virus from an endogenous source (17).

The studies from the pre-highly active antiretroviral therapy era have shown that adenoviruses caused active infection in 12% of AIDS patients and 45% of these infections caused death within 2 months (15). Children, in whom primary infections occur, are particularly susceptible to adenovirus disease if immunosuppressed. Forty-nine (10%) children in a series of 484 pediatric liver transplant recipients had an adenovirus isolated from their liver, lungs, or gastrointestinal tract. Twenty (4%) of these children developed invasive adenovirus infection, which led to 9 (2%) deaths (20). Adenovirus infections occur in 5% to 27% of patients following hematopoietic stem cell transplantation (HSCT), with an associated mortality of up to 50% (7, 18, 26, 30).

Although nosocomial transmission of adenovirus is well documented in ophthalmology clinics (21), neonatal intensive care units (6), pediatric wards (14), and chronic psychiatric care facilities (16), no such transmission in a hematology unit has been reported. Here we report an outbreak of adenovirus infection in a hematology unit. The aims of this study were to investigate the nature of outbreak and to identify the source of infection and mode of its transmission. Further investigations were performed to study the molecular epidemiology of adenovirus infection in the hematology unit.

## MATERIALS AND METHODS

**Outbreak cohort.** From 4 March to 3 April 2002, there was an outbreak of diarrhea in one of the hematology wards in University College London Hospitals involving six patients. The first case of diarrhea was reported on 4 March. There were two more cases of diarrhea on 12 March, which led to declaration of a possible outbreak. The last case of outbreak was identified on 3 April (Fig. 1). Patient no. 1 was admitted to the ward on 4 March 2002 with diarrhea. All of the other five patients who developed diarrhea were in the ward for more than 2 weeks (data not shown). During the outbreak, 21 patients stayed in the ward for various lengths of time. Six (29%) were affected with diarrhea. All of these six patients (four men and two women) were adults (19 to 62 years old) and HSCT recipients (four allograft and two autograft). The clinical characteristics of these patients are shown in Table 1.

**Controls for molecular investigations.** One stool sample, which was collected during the outbreak period, from a healthy nonhospitalized child with adenovirus infection and 11 coded archival clinical isolates of adenovirus from Great Ormond Street Hospital (GOSH), London, United Kingdom, were included as controls in this study.

**Samples for routine surveillance for CMV infection.** Eighty-nine coded leftover consecutive plasma samples, collected between June 2001 and May 2002, from HSCT recipients for routine surveillance for cytomegalovirus (CMV) infection were also investigated for adeno-viremia and its clinical implications as a part of an ongoing audit to improve clinical management of patients in the hematology unit.

**Setting.** There are three wards on adjacent floors in the hematology unit at University College London Hospitals. The outbreak was limited to the ward on

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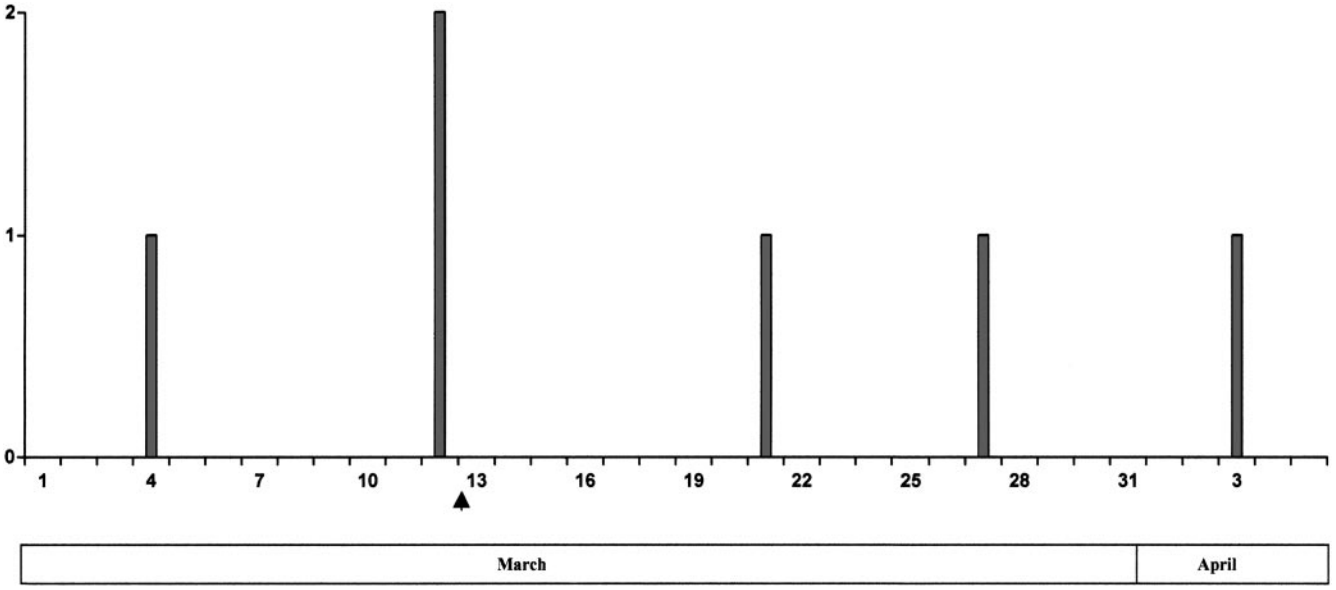


FIG. 1. Cases of diarrhea due to adenovirus infection. The arrow indicates the declaration of outbreak.

the middle floor. There are 12 single rooms, 1 double room, and a bay for four patients in this ward. Patients shared washing facilities and three toilets. Two patients affected with diarrhea were in a four-bed bay, one patient was in double room, and three patients were in single rooms. There are dedicated nursing staffs for each of the three floors, but a single team of doctors is responsible for the care of patients in the unit as a whole.

**Electron microscopy and virus isolation.** Adenoviruses were detected by electron microscopy of stool samples. Stool samples were also inoculated into primary rhesus monkey kidney cells (European Cell Culture Collection, Porton, Salisbury, United Kingdom) and human embryonic lung cells. The cytopathic effect seen in cell culture and the presence of adenovirus were confirmed by electron microscopy.

**Nucleic acid extraction.** Nucleic acid was extracted from stool samples, cell culture isolates, and EDTA plasma using a QIAamp DNA stool minikit, a QIAamp blood minikit, and a QIAamp 96 virus BioRobot kit, respectively, according to the manufacturer's protocols. DNA from stool samples and supernatant of cell cultures was extracted manually, and QIAGEN BioRobot 9604 (QIAGEN, Hilden, Germany) was used to extract DNA from plasma.

**PCR.** Each sample was investigated by a previously reported PCR assay targeting the hexon gene with some modifications (4). PCR was performed in a 50-μl volume containing either 5 μl of DNA extracted from stool or 20 μl of DNA extracted from plasma, 2.5 mM $MgCl_2$, 5 μl of GeneAmp 10× PCR buffer II, 0.25 unit of AmpliTaq Gold (Applied Biosytems), 200 μM of deoxynucleoside triphosphates, and 25 pmol of each primer. A clinical isolate of adenovirus was used as a positive control, and nuclease-free water was used as a negative control for DNA extraction and amplification. DNA from adenovirus type 2 from Sigma, St. Louis, Missouri, was used as an additional positive control for amplification. Samples and controls were denatured at 95°C for 5 min, followed by 40 cycles of amplification in an Applied Biosystems thermal cycler 480. Each cycle consisted of denaturation at 94°C for 30 s, annealing of primers at 55°C for 1 min, and extension at 72°C for 1 min followed by final extension at 72°C for 7 min. The size

TABLE 1. Clinical characteristics of patients with adenovirus infection[a]

| Patient no. | Age (yr) | Sex | Hematological disease | Nature of stem cell transplant | Adenovirus in blood[b] | Adenovirus in feces | GVHD | Clinical features at initial detection of outbreak strain | No. of days between adenovirus infection and transplant/outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 19 | Female | AML | T depleted, MUD | Yes | Yes | Yes | Respiratory failure, fever, and diarrhea | <100/died within 43 days of infection |
| 2 | 50 | Female | CLL | T depleted, SD | Yes | Yes | Yes | Fever and diarrhea | >100/survived |
| 3 | 53 | Male | Mantle cell lymphoma | Autologous | Not tested | Yes | No | Fever and diarrhea | <50/survived |
| 4 | 55 | Male | Multiple myeloma | T depleted, SD | Yes | Yes | Yes | Diarrhea, hepatitis, and posttransplant lymphoproliferative disorder | >100/died within 5 days of infection |
| 5 | 62 | Male | Diffuse large B-cell lymphoma | Autologous | Yes | Yes | No | Diarrhea | <50/survived |
| 6 | 37 | Male | AML | T depleted, MMUD | Yes | Yes | Yes | Fever and diarrhea | >100/survived |
| 7 | 44 | Female | NHL | T depleted, MUD | Yes | Not tested | No | Respiratory and hepatic failure[c] | <100/died within 3 days of infection |
| 8 | 50 | Male | Multiple myeloma | T depleted, SD | Yes | Not tested | No | Respiratory and renal failure[c] | <100/died within 2 days of infection |
| 9 | 48 | Male | Multiple myeloma | T depleted, MUD | Yes | Not tested | Yes | Multiorgan failure[c] | >100/died within 5 days of infection |

[a] Abbreviations: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; MUD, matched unrelated donor; SD, sibling donor; MMUD, mismatched unrelated donor; GVHD, graft-versus-host disease.

[b] Blood samples from patient no. 1, 2, 4, and 5 were collected during the outbreak. The blood from patient no. 6 was collected 23 days prior to outbreak.

[c] Patient no. 7, 8, and 9 were not part of the outbreak cohort.

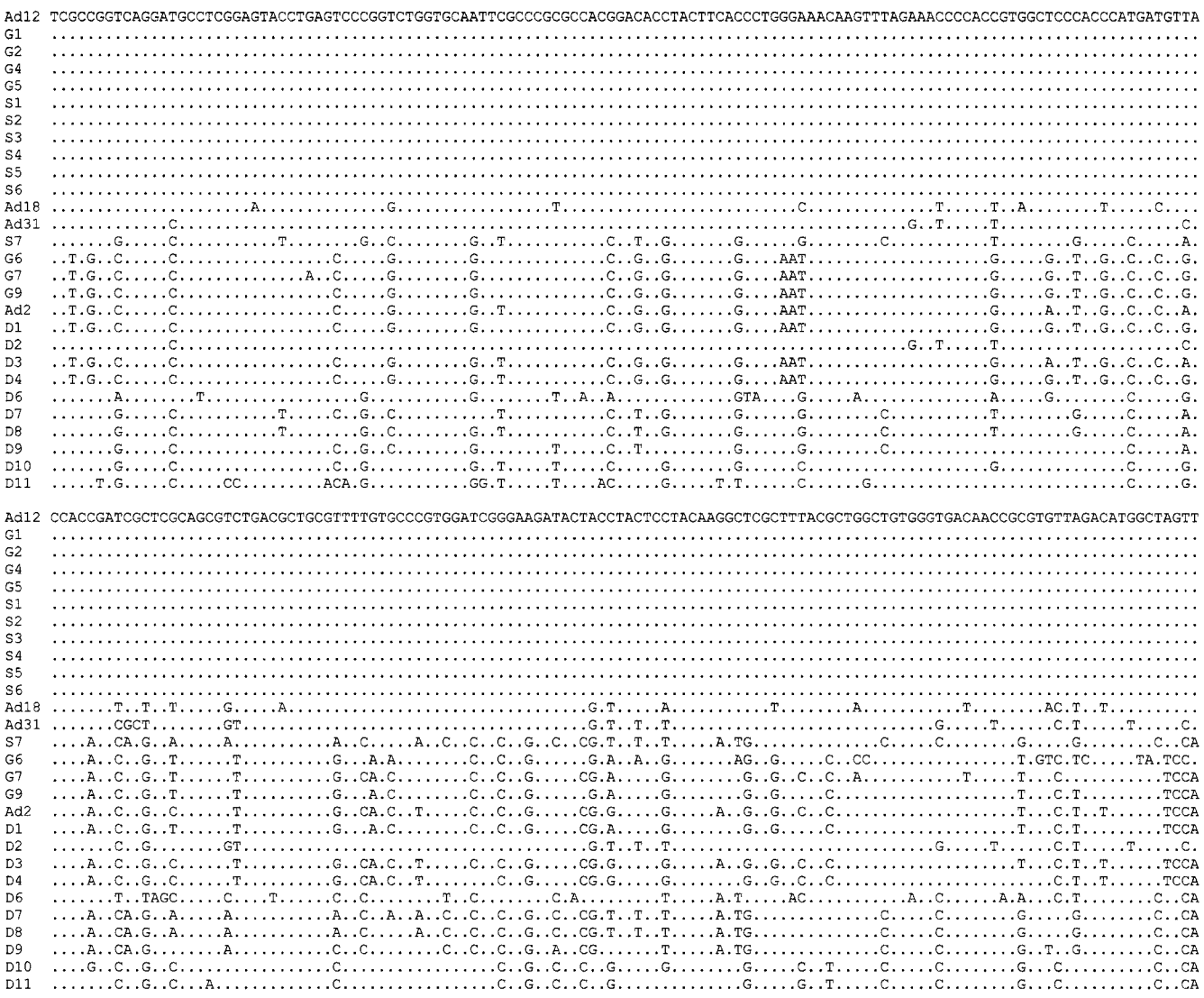

FIG. 2. Sequence alignment of amplicons generated by Allard's PCR. The primer binding sites are not shown. S1 to S6 and G1 to G6, amplicons from stool and plasma samples, respectively, from patients affected with the outbreak of diarrhea; G7 and G9, amplicons from plasma of HSCT recipients undergoing routine CMV surveillance; S7, amplicon from the stool of a healthy child; D1 to D11, amplicons from GOSH isolates; Ad2, amplicon from an isolate from Sigma; Ad12, X73487; Ad18, AF161575; Ad31, AF161576.

of amplicons was ascertained by gel electrophoresis using 1% agarose (SeaKems, Flowgen, Lichfield, Staffordshire, United Kingdom).

Six stool samples from the outbreak patients were also analyzed at GOSH using two previously described multiplex PCR assays, one for amplification of the hexon gene and the other for the fiber gene of adenovirus (24, 28).

**Sequencing and phylogenetic analysis.** Amplicons for sequencing were purified by using QIAquick spin columns, according to the manufacturer's protocol (QIAGEN, Hilden, Germany). The nucleotide sequences in both forward and reverse directions were determined by the dideoxy chain termination method using an Applied Biosystems ABI Prism 377 sequencer (Applied Biosystems, Foster City, Calif.). The Sequencher Programme (Gene Codes Corporation, Michigan) and PHYLIP package (version 3.6 Alpha 2) were used for DNA sequence alignments and phylogenetic analysis, respectively (11, 12).

## RESULTS

**Electron microscopy and virus isolation.** Electron microscopy and cell culture identified adenovirus in stool samples from all six patients suffering with diarrhea. Adenovirus grew in both primary rhesus monkey kidney and human embryonic lung cells. Stool samples were negative for adenovirus according to electron microscopy and cell culture from all 15 patients without diarrhea from the outbreak cohort.

**Molecular investigations.** Hexon gene amplicons were generated from the stools of six patients with diarrhea and one stool sample from a healthy nonhospitalized child. Hexon amplicons were also generated from 8 of 89 plasma samples. These samples were collected for routine CMV surveillance independent of the adenovirus outbreak. After breaking the code for blood samples, it transpired that five of these eight positive samples belonged to patients who were affected by outbreak, and four of these five samples were collected at the time when they were suffering with diarrhea. Amplicons were also generated from 11 adenovirus isolates from GOSH.

The nucleotide sequences of amplicons were aligned, and a

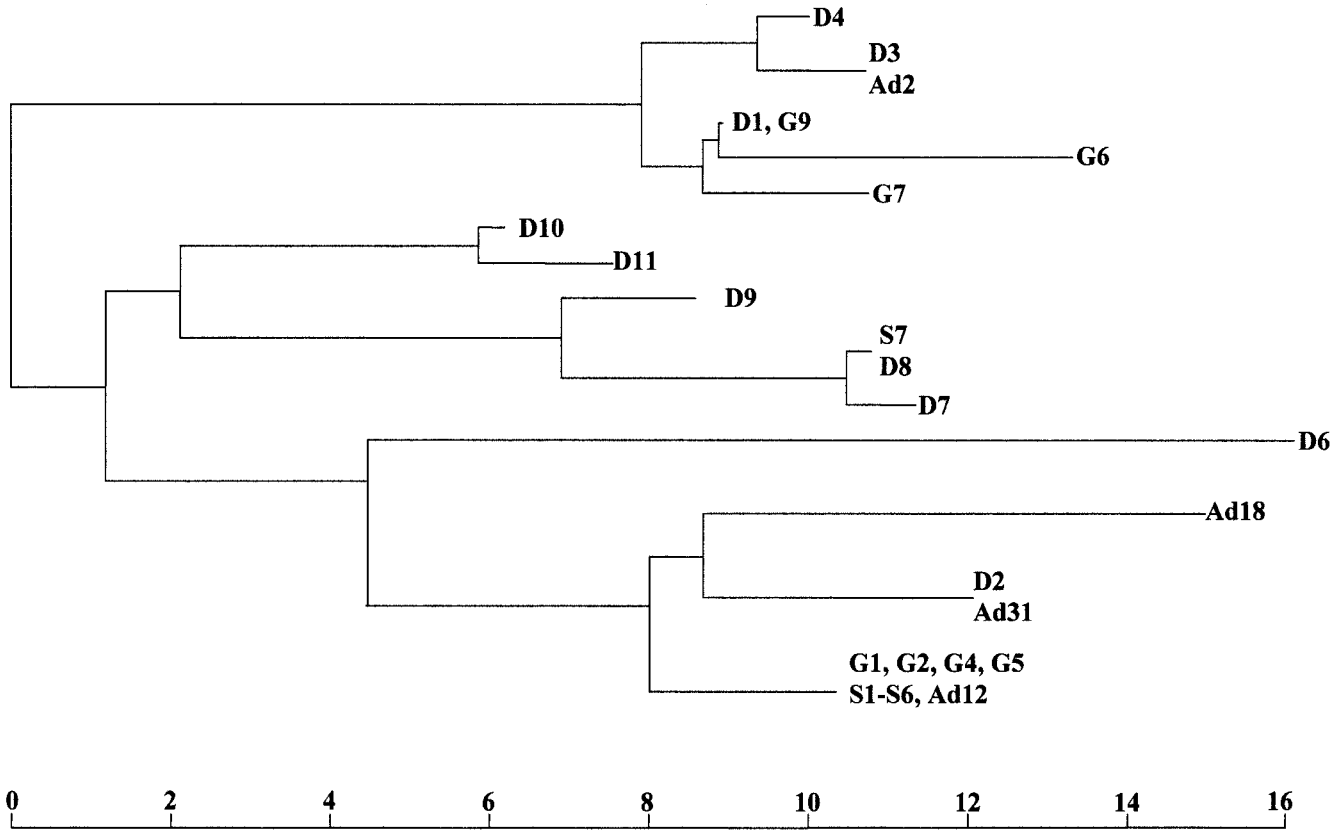


FIG. 3. Phylogenetic tree based on sequence alignment of amplicons. The scale bar indicates relative genetic distance according to the Jukes-Cantor algorithm. S1 to S6 and G1 to G6, amplicons from stool and plasma samples, respectively, from patients affected with the outbreak of diarrhea; G7 and G9, amplicons from plasma of HSCT recipients undergoing routine CMV surveillance; S7, amplicon from the stool of a healthy child; D1 to D11, amplicons from GOSH isolates; Ad2, amplicon from an isolate from Sigma; Ad12, X73487; Ad18, AF161575; Ad31, AF161576.

phylogenetic tree was generated using neighbor-joining analysis (Fig. 2 and 3). The six outbreak stool sample amplicons, S1 to S6, clustered together on a single branch, together with four of the five corresponding plasma samples amplicons, G1, G2, G4, and G5. An exception was the plasma amplicon G6 from patient no. 6, which clustered on a genetically distant branch from the above samples. The G6 plasma sample was collected 23 days prior to when patient no. 6 developed diarrhea. A blood sample from patient no. 3 was not available. G7, G8, and G9 were 3 of 89 plasma samples from HSCT recipients, which were positive for adenovirus DNA. These three patients were not part of the outbreak cohort. S7 was an amplicon from a nonhospitalized immunocompetent child with diarrhea.

The archival isolates from GOSH, D1 to D11, both were phylogenetically distinct from the outbreak strain and formed a tree topology consistent with previous multiplex subgrouping PCR performed at GOSH (24, 28). All six isolates from patients affected with the outbreak of diarrhea were reported to belong to group A, either type 12 or 18, by independent investigations performed at GOSH. On BLAST search (5), the amplicon generated from the outbreak strain showed 100%, 93%, and 90% homology with adenovirus types 12 (accession no. X73487), 31 (AF161576), and 18 (AF161575), respectively. Although the sequence information for the identity of the outbreak stain was limited, it raised a strong possibility that this strain was type 12. Amplicons from samples G8 and D5 are not shown in Fig. 2 and 3 due to poor quality of sequence data.

## DISCUSSION

Adenovirus is an extremely hardy virus. The infectivity of desiccated adenovirus from a nonporous surface was documented for up to 35 days (23). The shedding of virus especially from the gastrointestinal tract (13) and respiratory tract (10) may continue for months after initial infection. Close contact with individuals in crowded places increases the risk for infection. Prolonged shedding of virus especially from immunocompromised hospitalized patients and its hardy nature make it an ideal agent for nosocomial transmission. However, such transmission in any hematology unit has not been documented.

The virus neutralization assay has been extensively used to type adenovirus from clinical specimens. This method is laborious, needs growth of virus in cell culture, is limited due to an absence of specific antisera against previously unidentified types, and occasionally generates incorrect results due to cross-reactivity of antibodies between various types. In an outbreak of epidemic keratoconjunctivitis, the outbreak strain was wrongly identified as type 10 by neutralization assay but proved to be type 37 after restriction fragment length polymorphism (RFLP) (9). A number of molecular techniques have been

used for genotyping of adenovirus isolates, i.e., RFLP of whole virus genome (2), RFLP analysis of amplicons (RFLP-PCR) generated from hexon (3) and fiber (1) genes, and multiplex subgenus type-specific PCR (22, 24, 28, 29). Molecular assays are more accurate and discriminatory in typing, are less laborious, and have shorter turnaround time compared to neutralization assay. Comparison of the amino acid sequences of 15 hexon proteins from different subgenera of adenovirus has revealed seven discrete hypervariable regions among the 250 variable residues in loops 1 and 2. These regions differed in length between serotypes, from 2 to 38 residues, and contained >99% of hexon serotype-specific residues among human serotypes (8). This genetic characteristic of the hexon gene was exploited to investigate the outbreak of diarrhea due to adenovirus infection. Comparison of the nucleotide sequences of amplicons derived directly from clinical specimens has not been used previously to investigate an adenovirus outbreak. Amplicons generated from the hexon gene provided sufficient genetic information to investigate the nature of this outbreak. Nucleotide sequence comparison strongly suggested that all six patients with diarrhea had the same strain of adenovirus in their stool samples, and four of these patients had the outbreak strain in their blood, confirming nosocomial transmission of infection. Patient no. 6 had the outbreak strain in his stool but a different strain in his blood. This blood sample was collected 23 days before he developed diarrhea, suggesting an episode of adenovirus reactivation and viremia independent of the outbreak.

The source of outbreak appears to be patient no. 1, who was admitted to the hematology unit on 4 March with diarrhea. Her graft was from a matched unrelated donor. She was within 100 days of her transplant and was on immunosuppressive therapy. Considering her immune status, the probable source of adenovirus in this patient was activation of an endogenous infection. Review of her clinical records showed the presence of adenovirus in her stool in a sample that was collected on 13 February 2002. This isolate was not available for molecular investigations. The subsequent five patients who developed diarrhea were in the ward for more than 2 weeks before they developed diarrhea, suggesting nosocomial transmission of infection. The role of health care workers in transmission of infection was not investigated. The shared washing and toilet facilities may have had a role in the spread of infection, especially as the index case was at times incontinent of feces. However, this possibility was not investigated, i.e., by performing PCR on swabs from surfaces of washing facilities.

Adenovirus DNA was detected in 8 (9%) of 89 plasma samples. The detection of adenovirus DNA in plasma suggested active replication of the virus. Most of these patients had features of disseminated infection, and four of them died within a week of detection of adenovirus in their blood (Table 1). It is difficult to assess the role of adeno-viremia in morbidity and mortality of these patients due to a number of limitations in this study, i.e., availability of a single plasma sample, lack of quantification of adeno-viremia, and absence of histological or postmortem information and contribution of other infections, e.g., CMV and Epstein-Barr virus. Comparison of the nucleotide sequences of amplicons generated directly from clinical samples proved useful to identify the nosocomial transmission of infection from a single source in this outbreak. The standard infection control measures were effective to manage this outbreak. Further studies are needed to examine the value of routine surveillance of adenovirus viremia in HSCT recipients.

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